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Serial Examination of 20,248 Newborn Fetuses and Infants: Correlations Between Drug Exposure and Major Malformations

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Maternal medication during the first trimester of pregnancy has been discussed as a risk factor for development of birth defects. The correlation between maternal drug use and major malformations was investigated in a population-based case-control study in Mainz. Over a period of 5 years (1990–1994), 20,248 livebirths, stillbirths, and abortions underwent physical and sonographic examination, and anamnestic data were collected. A total of 1,472 births with congenital anomalies (cases) and 9,682 births without major and minor malformations (controls) were analyzed. We distinguished between 30 different drug categories, which were divided into medication taken continuously (before and during pregnancy; CM) and acute medication (drugs given within the first 3 months of gravidity; AM). Statistically highly-significant results [CM: Odds Ratios (OR) 1.2, Confidence Intervals (CI) 1.1–1.4, $P = 0.008$; AM: OR 1.2, CI 1.1–1.3, $P = 0.008$] were established for maternal drug use in correlation to birth defects. For the majority of combinations between drugs and specific malformations no teratogenic risks were found. However, statistically significant associations were recorded for antiallergics and heart anomalies (CM, AM) as well as musculoskeletal anomalies (AM); for bronchodilators and heart anomalies (CM, AM); for antiepileptics and anomalies of the internal urogenital system (CM), as well as cleft palate/cleft lips (AM); for thyroid hormones and anomalies of the nervous system (CM, AM), as well as anomalies of the external urogenital system (CM, AM); for insulin and anomalies of the musculoskeletal system (CM); for digitalis and anomalies of the musculoskeletal system (AM).

KEY WORDS: congenital anomalies, drug use in pregnancy, teratogens, epidemiology

INTRODUCTION

The Mainz birth defect monitoring system, the "Mainzer Model," was launched in 1990. It was the aim of this screening project to determine incidences and etiological causes of congenital birth defects and to establish preventive measures.

All neonates born in Mainz therefore underwent a standardized physical and sonographic examination. Anamnestic data of family history, medication during pregnancy, profession of the parents, course of pregnancy, environmental factors, drug exposure, etc., were collected. To determine risk factors, we used population-based case-control studies to investigate a possible relationship between morphological defects and anamnestic data.

Since the occurrence of the thalidomide tragedy, a number of drugs given to pregnant women have been reported to act as possible teratogens [Lenz, 1988; Shepard, 1986]. Additional drugs, e.g., warfarin, retinoic acid, and hydantoin, are also known teratogens [Carson and Reid, 1976; Ornoy and Arnon, 1993; Hanson and South, 1975]. The effect of drug exposure depends on the pharmacologic components of the drugs, on metabolic components of mother and child, and on gestational age [Füllgraff and Palm, 1992; Opitz, 1994]. The development of the unborn child has been divided into the following stages: embryogenesis [till end of week 8 post conception (p.c.)] and phenogenesis (till end of week 38 p.c.). Embryogenesis is subdivided into blastogensis (first 4 weeks of development) and organogensis (second 4 weeks of development). Embryogenesis has been designated as a critical period of pregnancy, during which organogenesis takes place

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

and almost all teratogenic substances exert a major influence [Opitz, 1994, 1995]. A well-documented and impressive example is the effect of thalidomide, in particular for multiple malformations caused by the same drug at different time periods [Fraser, 1988; Majewski, 1977].

The first 3 months of pregnancy are thus the most important period for teratogenic influences. We therefore undertook an analysis of the medications taken by pregnant women during this sensitive phase.

On the basis of case-control analyses we investigated: 1) if well-known teratogenic drugs were avoided in pregnant women; 2) if published associations between malformations and drug intake could be confirmed; and, most importantly, 3) if new correlations could be established between drug exposure and major malformations.

MATERIALS AND METHODS

From 1990–1994 we used a standardized procedure to examine 20,248 newborns (19,945 livebirths, 121 stillbirths, and 182 spontaneous abortions >15th week of gestation, as well as induced abortions). Stillbirths were defined as death after 20 weeks of gestation for a fetal weight of >500 g. Unfortunately, we were unable to include in the study spontaneous abortions between conception and a gestational age of <15 weeks because in almost all cases no pathological data were available.

All examinations were performed in the first week of life by four pediatricians trained in clinical genetics. For stillbirths and abortions, we used pathological findings instead of clinical and sonographic results. Chromosomal studies were done on all newborns with clinical signs of chromosomal aberrations, and on the majority of all malformed fetuses. During the period of our investigation, 21,278 livebirths and stillbirths (figures reported by the local birth registry office) were recorded in Mainz; 20,066 (94.3%) underwent our clinical examination and anamnestic data collection, respectively [Queißer-Luft et al., 1994].

We looked primarily for major malformations. These birth defects were defined according to EUROCAT [Eurocat report 6, 1995] and the International Clearinghouse for Birth Defects Monitoring Systems [International Clearinghouse for Birth Defects Monitoring Systems, 1991]. The malformations were divided into 10 organ categories: musculoskeletal anomalies, anomalies of the internal urogenital system, heart anomalies, anomalies of the external urogenital system, digestive system anomalies, nervous system anomalies, chromosomal anomalies, cleft palate/cleft lips, ear anomalies, and eye anomalies.

To obtain information about the medications taken by the mothers, we used two sources of information: the health report of the gynecologist, and anamnestic data recorded by the delivery-hospital staff approximately 6 weeks prior to birth. We were thus able to evaluate the validity of the data used to serve as the basis of our investigation.

We distinguished between 30 different categories (Table I) of drugs. All 30 categories were subdivided into medications taken continuously (before and during the entire period of gravidity) and acute medication, i.e., drugs given in the first 3 months of pregnancy. Iron and magnesium intake as well as combinations of different drug categories were excluded.

TABLE I. Baseline Numbers of Maternal Drug Intake for Specific Drug Categories Divided Into Continuous or Acute Medication*

	Medication number	
Drug category	Continuous	Acute
Analgesics	5	11
Antiallergics	40	28
Antiarrhythmic drugs	2	—
Antibiotics	9	120
Antiepileptics	42	31
Antihypertensives	31	22
Antihypotensives	31	55
Anticoagulants	9	9
Antirheumatics	1	—
Beta-blockers	46	38
Bronchodilators	49	53
Corticoids	29	28
Diuretics	2	2
Fibronlytic agents	—	2
Hypnotics/sedatives	6	5
Immunosuppressants	3	3
Cardiacs/digitalis	5	5
Coronary vasodilators	—	—
Psychopharmacologic agents	14	9
Thyroid hormones	566	410
Thyroid depressants	17	10
Sera/vaccines	1	—
Spasmolytics	3	—
Clotting inhibitors	2	3
Antituberculotics	1	—
Vitamins	19	1,210
Cytostatic agents	—	—
Insulin	73	55
Hormones/contraceptives	4	49
Calcium	4	39
Total	1,014	2,197

*Study population: 20,248, Mainz, 1990–1994.

In retrospective population-based case-control studies, we investigated maternal drug use as a possible teratogen factor. Cases consisted of all neonates with at least one major malformation (n = 1,472); controls consisted of all healthy newborns (n = 9,682) without any major or minor malformation. Exposure was defined as drug intake.

Comparisons between cases and controls with respect to drug exposure were made using standard logistic regression models [Breslow and Day, 1980; Henekens and Burin, 1987]. These models were used to derive odds ratios (OR) as approximation of relative risk and 95% confidence intervals (CI). Additionally, Fisher's exact test was calculated for very small numbers (<5) of exposed cases. The risk-odds ratio is the ratio of the odds in favor of getting disease, if exposed, to the odds in favor of getting disease if not exposed.

The analysis was performed in three steps:

1) Case-control studies for drug intake without subcategories and major malformations without subcategories.
2) Case-control studies for all 30 drug categories and all major malformations without subcategories.

3) Case-control studies for all 30 drug categories and major malformations divided into 10 organ categories.

RESULTS

Over the period from 1990–1994, we examined 20,248 newborns, stillbirths, and abortions: 1,472 children (7.3%) had major malformations. The incidence of malformations (per 10,000 births; diagnosis-based distribution) observed in the individual organ categories was as follows: musculoskeletal anomalies (258/10,000 births), anomalies of the internal urogenital system (145), heart anomalies (116), anomalies of the external urogenital system (61), digestive system anomalies (59), nervous system anomalies (49), chromosomal anomalies (38), cleft palate/cleft lips (35), ear anomalies (9), and eye anomalies (8).

One thousand and fourteen (5.0%) pregnant women received continuous medication (CM) and 2,197 (10.9%) received acute medication (AM) as monotherapy in the first trimester of gestation. The number of pregnant women receiving either CM or (AM) is shown in Table I. The five most frequently-administered categories of continuous medication included thyroid hormones, insulin, bronchodilators, antiepileptics, and antiallergic agents, while the most frequently-given acute medication categories comprised vitamins, thyroid hormones, antibiotics, insulin, and antihypotensives.

Coronary vasodilators and cytostatic agents were not prescribed or used in this study. No major malformations were observed for the categories of analgetics, antiarrhythmic drugs, anticoagulants, antirheumatics, diuretics, fibrinolytic agents, hypnotics/sedatives, immunosuppressants, psychopharmacologic agents, thyroid depressants, sera/vaccines, spasmolytics, clotting inhibitors, antituberculotics, and calcium. No case-control analyses were calculated for these drug categories.

As a first step we attempted to confirm whether drug exposure in fact represents a teratogen factor. Therefore, case-control analyses were performed for drugs and major malformations. Neither drugs nor malformations were divided into subgroups. These analyses allowed the confirmation of the expected statistically significant results.

The odds ratio for continuous medication (CM) during pregnancy and major malformations as well as that for acute medication (AM) and major malformations in the first trimester showed the following statistically highly-significant results: CM, OR 1.2 (CI, 1.1–1.4; $P = 0.008$), and AM, OR 1.2 (CI 1.1–1.3; $P = 0.008$).

Drug intake throughout pregnancy, excluding the first trimester of gravidity, did not result in an increased risk of malformations and was thus not statistically significant (OR 0.8; CI 0.6–1.4; $P = 0.48$); continuous drug intake, excluding the first trimester of pregnancy, showed the following results: OR 1.0 (CI, 0.8–1.3; $P = 0.89$). These results emphasize the significant correlation between drug use during the first 3 months of gestation and major malformations.

Table II shows the results of the case-control analyses for the 30 drug categories (CM and AM) and the major malformations without subcategories. In contrast to expectations, there were no increases in relative risks and no statistically significant results. The only findings of interest were slightly elevated values for CM and AM, i.e., continuous medication: antihypertensives (OR 1.1; CI 0.3–4.5), antihypotensives (OR 1.1; CI 0.3–4.4) and beta adrenergic blocking agents (OR 1.1; CI, 0.3–3.4); acute medication: antihypertensives (OR 1.6; CI, 0.2–11.3) and antihypotensives (OR 4.0; CI, 0.6–28.9).

The second step of our analysis consisted of the performance of case-control studies for the 30 drug categories and major malformations divided into 10 organ categories (musculoskeletal anomalies, anomalies of the internal urogenital system, heart anomalies, anomalies of the external urogenital system, digestive system anomalies, nervous system anomalies, chromosomal anomalies, cleft palate/cleft lips, ear anomalies, and eye anomalies). Table III depicts the statistically significant increased odds ratios for continuous and acute medication. Correlations were established between continuous drug intake (CM) and major malformations for the following organ categories: heart anom-

TABLE II. Odds Ratios With 95% Confidence Intervals for Drug Categories (Continuous Medication or Acute Medication) and Major Malformations Without Subcategories*

	Continuous medication		Acute medication	
Drug category	OR	CI	OR	CI
Antibiotics			0.7	0.4–1.4
Antiallergics	0.5	0.2–1.3	0.4	0.2–1.4
Antiepileptics	0.5	0.2–1.4	0.7	0.2–2.3
Antihypertensives	1.1	0.3–4.5	1.6	0.2–2.3
Antihypotensives	1.1	0.3–4.5	4.0	0.6–28
Beta-blockers	1.1	0.3–3.4	0.9	0.3–2.8
Bronchodilators	0.3	0.2–0.7	0.4	0.2–0.7
Corticoids	1.0	0.2–4.2	1.0	0.2–4.0
Cardiacs/digitalis			0.3	0.1–2.6
Thyroid hormones	1.0	0.7–1.4	0.9	0.6–1.3
Insulin	0.7	0.3–1.5		
Hormones/contraceptives	0.2	0.1–2.1	0.6	0.3–1.6
Vitamins			1.0	0.8–1.4

*Total cases = 1,472 and total controls = 9.682, Mainz, 1990–1994.

TABLE III. Increased Odds Ratios With 95% Confidence Intervals for Major Malformations Divided Into Organ Categories and Drug Categories (Continuous Medication or Acute Medication) Reaching Statistical Significance, Mainz, 1990–1994

Organ category malformation	Drug category	Continuous medication		Acute medication	
		OR	CI	OR	CI
Heart	Antiallergics	7.2	1.7–30	9.5	2.5–4.5
	Bronchodilators	5.8	1.4–24	5.3	1.3–22
Musculoskeletal system	Insulin	4.0	1.5–11		
	Digitalis			34	3.8–305
	Antiallergics			5.3	1.2–22
Internal urogenital system	Antiepileptics	4.4	1.1–18		
External urogenital system	Thyroid hormones	3.2	1.6–6.3	3.9	1.9–8.0
Nervous system	Thyroid hormones	2.9	1.2–7.3	4.1	1.6–10
Cleft palate/cleft lips	Antiepileptics			11.6	1.6–86

alies and antiallergics (OR 7.2; CI, 1.7–3.0; $P = 0.03$) as well as bronchodilators (OR 5.8; CI, 1.4–24; $P = 0.05$), anomalies of the internal urogenital system and antiepileptics (OR 4.4; CI, 1.1–18; $P = 0.05$), musculoskeletal anomalies and insulin (OR 4; CI, 1.5–11; $P = 0.02$), anomalies of the external urogenital system and thyroid hormones (OR 3.2; CI, 1.6–6.3; $P < 0.001$), and nervous system anomalies and thyroid hormones (OR 2.9; CI, 1.2–7.3; $P = 0.03$).

Combinations between acute mediation (AM) and specific organ defects showed the following results: heart anomalies and antiallergics (OR 9.5; CI, 2.5–45; $P = 0.02$) as well as bronchodilators (OR 5.3; CI, 1.3–22; $P = 0.05$), musculoskeletal anomalies and digitalis (OR 34; CI, 3.8–305; $P = 0.03$) as well as antiallergics (OR 5.3; CI, 1.2–22; $P = 0.05$), cleft palate/cleft lips and antiepileptics (OR 11.6; CI, 1.6–86; $P = 0.05$), anomalies of the nervous system and thyroid hormones (OR 4.1; CI, 1.6–10; $P = 0.01$), and anomalies of the external urogenital system and thyroid hormones (OR 3.9; CI, 1.9–8.0; $P < 0.001$).

Both types of drug intake (CM and AM) during the first 3 months of pregnancy led to almost similar results, while the values in the AM group were more representative. Our results showed statistically significant correlations between the intake of antiallergics, bronchodilators, thyroid hormones, antiepileptics, and insulin and specific major malformations. The investigated drugs may thus exert teratogenic effects.

Table IV depicts the combinations between major malformations (divided into organ categories) and drug intake, which reached neither statistical significance nor elevated odds ratios. For continuous medication we observed 14 associations, and for acute medication 26 associations. Mainly, thyroid hormones, vitamins, and antibiotics were found to be medications without teratogenic risks.

In addition to the described statistically significant increased relative risks (Table III) and the values recorded for drugs which were shown to have no teratogenic effect (Table IV), we obtained a number of significant results on increased relative risks which, however, did not reach statistical significance (Table V). The latter consisted primarily of those case-control analyses where the number of exposed patients with malformations ranged below 3. On the basis of the small numbers of exposed cases no statistical significance could be reached.

Table V shows the increased, but statistically not significant, odds ratios for continuous and acute medication in the first trimester of pregnancy. Correlations were established between continuous drug intake (CM) and major malformations for the following organ categories: digestive system anomalies and 1) corticoids (OR 8.4; $P = 0.11$), 2) antiepileptics (OR 5.7; $P = 0.16$), 3) beta blockers (OR 5.2; $P = 0.18$), and 4) bronchodilators (OR 4.9; $P = 0.19$); chromosomal anomalies and 1) antiallergics (OR 6.8; $P = 0.14$), 2) bronchodilators (OR 5.5; $P = 0.17$), and 3) insulin (OR 4.8; $P = 0.19$); and cleft palate and cleft lips and 1) antiepileptics (OR 8.5; $P = 0.11$), and 2) bronchodilators (OR 7.2; $P = 0.13$); musculoskeletal anomalies and antiallergics (OR 3.6; $P = 0.11$).

Combinations between acute medication (AM) and specific organ defects showed the following results: digestive system anomalies and 1) corticoids (OR 8.7; $P = 0.11$), 2) antiepileptics (OR 7.8; $P = 0.12$), and 3) bronchodilators (OR 4.5; $P = 0.20$); chromosomal anomalies and hormones (OR 5.5; $P = 0.17$), as well as bronchodilators (OR 5.1; $P = 0.13$); cleft palate/cleft lips and bronchodilators (OR 6.7; $P = 0.14$) as well as insulin (OR 6.4; $P = 0.14$); musculoskeletal anomalies and bronchodilators (OR 2.7; $P = 0.11$) as well as insulin (OR 2.6; $P = 0.18$); ear anomalies and antibiotics (OR 9.4; $P = 0.10$); heart anomalies and thyroid hormones (OR 2.0; $P = 0.13$); nervous system anomalies and hormones (OR 6.6; $P = 0.14$); and anomalies of the external urogenital system and antibiotics (OR 3.2; $P = 0.13$).

For both types of drug intake (CM and AM), we observed almost identical combinations of drugs and specific organ defects. Out of the 30 drug categories investigated, we found the following to have possible teratogenic effect: antiallergics, antiepileptics, bronchodilators, beta-blockers, thyroid hormones, corticoids, insulin, sexual hormones, and antibiotics. Correlations were established primarily for anomalies of the diges-

TABLE IV. Odds Ratios With 95% Confidence Intervals for Major Malformations Divided Into Organ Categories and Drug Categories (Continous Medication or Acute Medication) Not Reaching Statistical Significance*

Organ category malformation	Drug category	Continuous medication		Acute medication	
		OR	CI	OR	CI
Digestive system	Thyroid hormones	0.4	0.1–2.9	0.6	0.1–4.0
	Antibiotics			2.0	0.3–14
	Vitamins			1.8	0.8–3.6
Chromosomes	Thyroid hormones	1.4	0.4–4.5	1.3	0.3–5.3
	Antibiotics			2.2	0.3–1.6
	Vitamins			0.4	0.1–1.7
Cleft palate/cleft lips	Thyroid hormones	0.6	0.1–4.2		
	Vitamins			1.5	0.6–3.7
Musculoskeletal system	Antiepileptics	1.7	0.2–12	2.3	0.3–17
	Beta-blockers	1.5	0.2–11	1.9	0.3–13
	Bronchodilators	2.9	0.6–12		
	Corticoids	2.4	0.3–18	2.5	0.3–19
	Thyroid hormones	1.2	0.7–2.3	1.0	0.5–2.3
	Vitamins			0.8	0.5–1.4
	Hormones/contraceptives			1.4	0.2–10
Ear	Thyroid hormones	1.9	0.3–15	2.7	0.4–20
	Vitamins			1.9	0.4–8.0
Heart	Thyroid hormones	0.7	0.2–2.2		
	Antibiotics			1.1	0.2–8.2
	Vitamins			0.9	0.4–1.8
Nervous system	Vitamins			0.8	0.2–2.4
External urogenital system	Insulin	2.6	0.4–19	3.4	0.5–25
	Vitamins			0.9	0.4–2.1
	Hormones/contraceptives			3.9	0.5–28
Internal urogenital system	Antihypertensives	2.9	0.4–21		
	Antihypotensives			1.6	0.2–11
	Thyroid hormones	0.8	0.3–1.9	0.9	0.3–2.3
	Insulin	2.5	0.6–10	1.6	0.2–11
	Vitamins			0.9	0.5–1.7
Eye	Vitamins			2.3	0.4–8.0

*$P > 0.2$. Mainz, 1990–1994.

tive system, the musculoskeletal system, the heart, chromosomes, and cleft palate/cleft lips.

DISCUSSION

In this study we analyzed the physical and anamnestic data of 20,248 newborns, stillbirths, and abortions. One thousand and fourteen (5.0%) mothers received continuous, and 2,197 (10.9%) acute, medication during the first trimester of pregnancy, i.e., maternal drug use in our population reflected a generally cautious attitude during this phase of gestation. A search of the available literature revealed that from 30–50% of women use drugs during the first 3 months of pregnancy [Jick et al., 1981; Rubin et al., 1993; Simpson et al., 1989]. In these studies, the entire maternal drug use—not only continuous and acute medication, but also the sporadic use of single doses of specific drugs and combinations of several drug categories—was considered. However, the allocation of drug categories made by these authors is similar to that of our study.

We present here an overview of the most relevant data obtained by our first analyses.

In case-control studies we found statistically highly-significant associations between drug exposure during the first trimester of gestation and major malformations. The same analyses were performed for maternal drug use during pregnancy, excluding the first trimester. The results of this investigation did not reach statistical significance. These data underline the important role of maternal drug use in the first 3 months of pregnancy [Khoury and Holtzman, 1987]. Although these results were not surprising, the comprehensive epidemiologic analyses for the entire 5-year period and the total population revealed a number of new aspects and statistically significant data regarding continuous and acute medication.

Case-control studies for the 30 drug categories and the major malformations (without subgroups) showed no statistical associations. Merely very slight increases in odds ratios for continuous medication and antihypertensives, antihypotensives, and beta-blockers, as well as acute medication and antihypertensives or antihypotensives, were observed. This supports the results reported by Cockburn et al. [1982] (malformations of the internal urogenital system and methyldopa), and by Duminy and Burger [1981], Knott et al. [1989], and Brent et al. [1993] (angiotensin converting enzyme [ACE]-inhibitors and malformations of the internal urogenital system and defects of ossification) for antihypertensives. For the categories of antihypotensives and beta-blockers, no markedly increased relative risks have been reported.

TABLE V. Increased Odds Ratios With 95% Confidence Intervals for Malformations Divided Into Organ Categories and Drug Categories (Continuous Medication or Acute Medication) Not Reaching Statistical Significance, $P < 0.2$, Mainz, 1990–1994

Organ category malformation	Drug category	Continuous medication		Acute medication	
		OR	CI	OR	CI
Digestive system	Corticoids	8.4	0.9–62	8.7	0.9–64
	Antiepileptics	5.7	0.8–42	7.8	0.9–58
	Beta-blockers	5.2	0.7–38		
	Bronchodilators	4.9	0.7–35	4.5	0.6–32
Chromosomes	Antiallergics	6.8	0.9–50		
	Bronchodilators	5.5	0.8–40	5.1	0.7–37
	Insulin	4.8	0.7–35		
	Hormones/contraceptives			5.5	0.8–40
Cleft palate/cleft lips	Antiepileptics	8.5	0.9–62		
	Bronchodilators	7.2	0.9–53	6.7	0.9–49
	Insulin			6.4	0.9–47
Musculoskeletal system	Antiallergics	3.6	0.9–15		
	Bronchodilators			2.7	0.7–11
	Insulin			2.6	0.6–10
Ear	Antibiotics			9.4	0.9–71
Heart	Thyroid hormones			2.0	0.9–4.7
Nervous system	Hormones/contraceptives			6.6	0.9–48
External urogenital system	Antibiotics			3.2	0.8–13

The calculated odds ratios show that consideration of only the variable "major malformation" does not yield sufficiently accurate results. We therefore subdivided the major malformations into organ categories in order to obtain more accurate results. Calculating these case-control studies for the 30 drug categories and the 10 categories of major malformations, we obtained highly increased odds ratios which reached statistical significance, elevated odd ratios not reaching statistical significance, and relative risks without indications of teratogenic effects.

For the category of antiallergics we observed combinations with malformations of the heart and the musculoskeletal system, and chromosomal aberrations. Our results do not fully support those reported by Hill et al. [1988], who found no statistically significant relative risk for major malformations, or those obtained by Werler et al. [1992] for musculoskeletal defects in combination with antihistamines. There still is a paucity of available results with regard to this drug category [Witter et al., 1981]. Regarding the use of H1-receptor-blocking agents during pregnancy, undesirable cardiovascular effects and side effects on the nervous system could not be completely excluded [Simons, 1994]. Chromosomal defects combined with teratogenic effects of antiallergics have not been reported. The possibility that fetal anomalies are caused by the basic disease, in particular by the effect of hypoxemia, and not by the teratogenic influence of the medication, also needs to be considered [Greenberger and Patterson, 1983].

Antiepileptics and major malformations have been described as possible teratogenic factors [Hanson and South, 1975; Hill et al., 1988; Jones et al., 1989; Lindhout and Omtzigt, 1994; Little and Santos-Ramos, 1993; Meadow, 1991; Stickler et al., 1985; Treiman, 1993; Zackai et al., 1975]. These findings have been confirmed by our results. We found statistically significant combinations for antiepileptics and malformations of the internal urogenital system and cleft palate/cleft lips. The observed elevated relative risk for anomalies of the digestive system has not previously been reported. Treatments with a number of different drugs generally involve higher teratogenic risks [Kaneko et al., 1988] than the reported single-drug therapies. Genetic components and maternal basic disease may also exert important influences [Kelly et al., 1984; Kelly, 1984].

With a view to bronchodilators and major malformations, only limited results are available [Bachofen, 1986; Karlsson et al., 1980; Montella, 1992; Turner et al., 1980]. Associations between beta-sympatheticomimetics and cardial malformations have been discussed. Results obtained in animal trials showed atrial septum defects, atrial aplasias, arterial duct anomalies, and anomalies of the aortic arch [Hodach et al., 1975]. We noted statistically significant increases in odds ratios for heart anomalies and bronchodilators for continuous drug intake as well as for acute medication. These results are thus in concert with results reported in the literature. Further combinations with malformations of the digestive system, of chromosomes, of cleft palate/cleft lips, and of the musculoskeletal system were investigated. Similar results have not previously been discussed by other authors. Influences like hypoxia as a possible complication of maternal disease may act as further malformation-causing factors.

The use of digitalis glycosides during pregnancy is well-documented [Brady and Duff, 1989; Gianopoulos, 1989; Lee and Cotton, 1989], and related teratogenic influences have not been described. However, our results revealed a significant correlation between anomalies of the musculoskeletal system and digitalis application in

the first 3 months of gestation, while no increased risk for continuous use was noted. This leads us to assume that the acute disease of the mother in the first trimester or complications occurring in the course of the pregnancy may be the cause of the malformation.

An association between teratogenic effects and the administration of thyroid hormones cannot be excluded [Balen and Kurtz, 1990; Pekonen et al., 1984]. The majority of authors proceed on the assumption that hypothyroidism is a possible cause of malformations [Khoury et al., 1989; Potter, 1980]. Primarily, neural tube defects, cleft palate/cleft lips, chromosomal aberrations, and malformations of the musculoskeletal system have been reported. We found statistically significant values for CM and AM in combination with anomalies of the nervous system, and for CM and AM in combination with anomalies of the external urogenital system. Increased risks for mothers/unborn children under acute medication support the hypothesis of the influence exerted by a hypothyroid metabolic condition. In spite of this possibility, the teratogenic influence of thyroid hormones needs to be discussed, since we observed a statistically significant increase in the risk associated with the continuous use of thyroid hormones. Pregnant women who regularly receive thyroid hormones are generally under constant medical control before and during pregnancy to assure euthyroid metabolic conditions.

In our study, we found a statistically significant increased odds ratio for insulin application and malformations of the musculoskeletal system. Elevated risks were observed for chromosomal defects as well as for cleft palate/cleft lips. The combination of major malformations and the administration of insulin cannot be completely disregarded, but most authors view diabetes mellitus and not insulin as a risk factor [Cohen and Schenker, 1972; Miller et al., 1981; Mills, 1982; Molstedt-Pedersen, 1976; Soler et al., 1976]. In the literature, mainly malformations of the musculoskeletal system, the nervous system, heart defects, and cleft palate/cleft lips, as well as chromosomal aberrations, have been reported [Daw and Riley, 1984; Klingenberg et al., 1983; Kučera et al., 1965; Quaas et al., 1986; Schwaibold, 1985]. Results obtained by our study therefore corroborate those reported in the literature.

Chromosomal defects and anomalies of the nervous system were associated with increased odds ratios in combination with oral contraceptives (AM). Heart defects, malformations of the musculoskeletal system, and defects of the nervous system and gastrointestinal tract have been reported [Levy et al., 1973; Lammer and Codern, 1986; Nora et al., 1978]. Elevated correlations between chromosomal aberrations and oral contraceptives have not been noted.

Maternal use of antibiotics (AM) was found to carry increased risks of malformations for the external urogenital system and the ear. In contrast to results obtained by this study, the teratogenic risk involved in the use of antibiotic drugs during pregnancy was not found to be increased by other authors [Hill et al., 1988; Ornoy and Arnon, 1993; Wise, 1989; Werler et al., 1992]. Acute maternal use of antibiotics in combination with malformations gives rise to the hypothesis that infection occurring in the first 3 months of gestation causes congenital anomalies.

We observed elevated odds ratios for corticoids (CM, AM) and beta-blockers (CM, AM) in relation to malformations of the digestive system. Teratogenic influences cannot be excluded for corticoids [Fabel, 1988; Hill et al., 1988; Kitschke and Rümmerle, 1980; McDonald, 1994]. No increased risks were reported for the administration of beta-blockers [Rubin et al., 1993].

No indications of teratogenic effects were noted for vitamins (AM), thyroid hormones (CM, AM), antibiotics (AM), contraceptives (AM), and insulin (CM, AM) in combination with specific organ categories. These data are supported, e.g., by the results of Smithells et al. [1981] (for vitamins), Potter [1980] (for thyroid hormones), Carter and Wilson [1963], Werler et al. [1992], and Ornoy and Arnon [1993] (for antibiotics), Lammer and Codero [1986] and McDonald [1994] (for hormones), and Molstedt-Pedersen [1976] (for insulin).

Design and performance of this study excluded most of the theoretically possible biases. Definition biases, misclassifications, observation biases, and selection biases could thus be avoided. Possible flaws of this study may be seen in the absent inclusion of sporadic single doses of drug use in the first trimester of pregnancy, and lack of allocation of acute maternal drug use to exact day of gestation.

Our data show that well-known teratogens like warfarin, retinoic acid, hydantoin, etc., are not longer prescribed and used in pregnant women. In general, our study reflects a cautious attitude toward maternal drug use during the first trimester of pregnancy. The majority of drugs used by the mothers have not been shown to be associated with increased teratogenic risks and malformations of specific organ categories, e.g., multivitamins, thyroid hormones, and antibiotics.

A few possibly teratogenic agents, whose prescription and drug use could not be avoided in the first months of gestation, were noted. For this group we observed statistically significant correlations which are supported by results reported in the literature: antiallergics and heart defects; antiepileptics and malformations of the internal urogenital system as well as cleft palate/cleft lips; bronchodilators and cardial malformations; thyroid hormones and congenital anomalies of the nervous system; and insulin and malformations of the musculoskeletal system. For three of these six drug categories we also obtained statistically significant results in combination with specific organ categories that were not in concert with the data reported in the literature: antiallergics and malformations of the musculoskeletal system; digitalis glycosides and musculoskeletal defects; and thyroid hormones and malformations of the external urogenital system. These drug categories, as well as corticoids, beta-blockers, antibiotics, and oral contraceptives, were found to have markedly increased odds ratios in combination with specific birth defects. However, statistical significance was not reached. Nevertheless, between continuous and acute medication use there were no significant differences with regard to both drug and organ category.

Our findings emphasize the complexity of this area of research. Although a considerable number of studies have been performed to establish a relationship between drugs used during pregnancy and congenital malformations, and a cautious attitude towards drug prescription and maternal drug intake during the first trimester of gestation has evolved, additional combinations of drugs and birth defects continue to be observed. Further investigations are therefore required, especially in the areas of antiallergics, antiepileptics, bronchodilators, thyroid hormones, corticoids, and contraceptives.

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